REMARKS

Claims 1-4, 6-8 and 10 presently appear in this case. No claims have been allowed. The official action of February 24, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention is directed to methods for treating conditions wherein TNF is to be eliminated from the body or its effect in the body is to be antagonized by administering the TNF binding protein of the present invention.

Claims 3, 4, 7 and 8 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite, because it is unclear what "non-proteolytic protein" means. The examiner states that it might mean that the protein cannot be digested by protease, or alternatively that the protein lacks protease activity.

The claims have now been amended to specify that the protein does not have proteolytic activity. This is supported, for example, by the disclosure at page 13, lines 2-7. Since protease inhibitors do not interfere with the biological activity of the protein, it is clear that the protein does not have protease activity.

Claims 1-4, 6-8 and 10 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Seckinger in view of

Dayer. The examiner states that Seckinger discloses an inhibitory factor of TNF-α, but does not explicitly mention use of such a TNF inhibitor for treating conditions where TNF is to be eliminated or antagonized in order to inhibit the cytotoxic effect of TNF. The examiner states that Dayer teaches that TNF has been implicated in many conditions, and it would have been obvious to use the TNF-α inhibitor taught by Seckinger for the treatment of conditions wherein TNF is negatively involved, such as those taught by Dayer. This rejection is respectfully traversed.

The present invention would not have been obvious from any combination of Seckinger and Dayer, as Seckinger does not disclose any TNF-α inhibitory factor of sufficient purity to be used therapeutically. In this regard, the examiner's attention is invited to the fact that the present application is a divisional of application no. 09/414,609, now patent no. 6,479,632, which in turn was a divisional of application 08/474,691, which is now patent no. 5,981,701. In the latter patent, it was determined that the claim that is now patent claim 2 was not entitled to the effective filing date of the priority application, which would have antedated Seckinger. However, a prior art rejection over Seckinger was avoided by specifying in the claim that it was a substantially pure protein, and by proving during prosecution that the purity of

the protein obtained by the present invention was substantially greater than what could be obtained by Seckinger, and further in view of the fact that there was no indication in the prior art how one would have gone about further purifying the impure protein of Seckinger.

Attached hereto is a copy of a declaration under 37 C.F.R. §1.132 that was filed in grandparent application 08/474,691. This declaration was sufficient to convince the examiner to withdraw the rejection over Seckinger, and allow what now appears as claim 2 in the '701 patent. The declaration is by two of the present inventors, Dr. Hartmut Engelmann and Dr. David Wallach, who are also coauthors of the Engelmann et al 1989 publication, which is of record in this case. This declaration establishes that the purity obtained in the 1989 Engelmann publication is that which is expected from the method of the present specification, since both methods are the same. The purity obtainable by those methods is a specific activity of 600,000 units/mg. Note that the specification refers to the purity of these purification steps as being "substantially purified protein." Note paragraph 3, "Purification of the TNF Inhibitory Protein", bridging pages 15 and 16 of the present specification. Sub-paragraph (b), at the bottom of page 15, refers to subjecting "said crude protein fraction of step (a)" to ion exchange chromatography

to obtain "partially purified active fractions of the TNF inhibitory protein". Step (c), at the top of page 16, discloses applying said partially purified active fractions of the TNF inhibitory protein from step (b) to reversed phase high pressure liquid chromatography to obtain "substantially purified active fractions of the TNF inhibitory protein". Thus, those of ordinary skill in the art reading the present specification would understand that the term "substantially purified" does not comprehend the purity obtained only by ion exchange chromatography, which is referred to as "partially purified" by the present specification.

Seckinger only obtains such partial purification. Seckinger refers to his material as "semi purified inhibitor" or "partially purified Sephadex S-200 urine". See the sentence bridging pages 1512-1515; see also Table 1. Finally, note the first sentence of the discussion in Seckinger which states:

> We have found that when tested in a cytotoxicity assay, urine from febrile patients contained a TNF-α inhibitory activity whose nature remains to be determined by purification to homogeneity, many bands being still identified in SDS-PAGE of the Sephacryl S-200 fractions.

Thus, Seckinger concedes that many bands are identified and that purification to homogeneity is necessary for further characterization. Those of ordinary skill in the art would

not consider a partially purified protein to anticipate a substantially purified protein. The present inventors were the first to purify this TNF inhibitory protein to substantial homogeneity.

Once it was clear on the record from the attached declaration that the substantially purified protein of the present invention had a specific activity of 600,000, which is more than three orders of magnitude greater than that obtained by Seckinger, the examiner was convinced that Seckinger does not disclose the polypeptide required by the claim of that application that required that the polypeptides were substantially purified, particularly in the absence of evidence of record explaining why one of ordinary skill in the art in 1988 would have found it obvious how to purify such a crude partially purified material to an additional 2000-fold purity to obtain a substantially purified protein with a specific activity of 600,000. There was no universal cookbook protocol that could be used to purify all proteins. Selecting the proper separation techniques and the proper conditions within the separation techniques did not involve mere routine experimentation, especially in the 1988 time frame. Accordingly, the very substantial additional purification needed to obtain the substantially purified protein claimed claim 2 of the '701 patent not only differentiated the

partially purified proteins of Seckinger, but also established obviousness thereover.

The present claims are effectively directed to a method of use of the allowed protein claims in the parent patents. As indicated above, in the parent and grandparent cases, even those claims that were not entitled to the effective filing date of the Israeli priority application, such that Seckinger was available as a reference, were found to be patentable over Seckinger because it was only a very crude protein mixture. All of the present claims have now been amended to specify that the protein used in the present method is one that had previously been substantially purified. The words "previously been" have been used in order to avoid confusion when the substance is administered as a pharmaceutical composition. Clearly, substantially pure TBP-I (which is the name by which the protein of the present invention is presently known) will be mixed with a pharmaceutically acceptable excipient prior to administration. As the composition might not be considered to be substantially pure TBP-I, the language "which had previously been substantially purified" is used. Thus, it must be a substantially purified protein that is mixed with the carrier before being administered for the process of the claims.

The concept of mixing a purified protein with a pharmaceutical composition appears in the present specification. For example, in paragraph 83, on page 40, note the first sentence thereof, which speaks of pharmaceutical compositions with the substantially purified TNF inhibitory protein of the protein as active ingredient. Paragraph 84 on page 41 speaks of mixing the protein with physiologically acceptable carriers. Accordingly, the concept now appearing in the claims is present in the specification and, thus, it would be clear to anyone of ordinary skill in the art that the inventors were in possession of this aspect of the invention at the time of the effective filing date of the present application.

Accordingly, as all of the present claims require use of a substantially purified protein, and such a protein has already been found to be patentable over Seckinger in the parent and grandparent applications for the reasons discussed above, the present claims must also be patentable over Seckinger. Dayer adds nothing to the deficiencies of Seckinger, as discussed above. Thus, as Seckinger does not teach the TNF inhibitory protein of the present invention in substantially purified form as required by the present claims, this rejection must fall. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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